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(84) Title: COMBINATION OF AMANTADINE AND A TETRABENAZINE COMPOUND FOR TREATING HYPERKINETIC
DISORDERS

(57) Abstract: The present invention provides a method for treating a hyperkinetic movement disorder in a human patient. The
method comprises administering to a patient an effective amount of amantadine, or a salt thereof, and an effective amount of a tetra-
benazine compound selected from the group consisting of tetrabenazine, dihydrotetrabenazine, a salt thereof, an isomer thereof, and a
combination thereof. The methods of the present invention are particularly useful in treating chorea, tardive dyskinesia, or Tourette's
syndrome. The present invention further provides a pharmaceutical composition comprising an effective amount of amantadine and
an effective amount of a tetrabenazine compound.



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COMBINATION OF AMANTADINE AND A TETRABENAZINE COMPOUND FOR TREATING HYPERKINETIC DISORDERS

FIELD OF THE INVENTION

5 The present invention relates to a method for treating a hyperkinetic disorder in a human patient by administering to a patient a combination of amantadine and a tetrabenazine compound. The invention also relates to a pharmaceutical composition comprising amantadine and a tetrabenazine compound.

10 BACKGROUND OF THE INVENTION

Hyperkinetic movement disorders are generally characterized by involuntary, purposeless movements that flow randomly from one body part to another. There are approximately 350,000 people affected by hyperkinetic movement disorders in the United States and Canada. There are currently no FDA-approved treatments for hyperkinetic
15 movement disorders in the United States. One of the hyperkinetic movement disorders is chorea, which is characterized by brief, irregular contractions that are not repetitive or rhythmic, but appear to flow from one body part to the next, and which can occur with slow, twisting and writhing movements called athetosis. Huntington's disease is a progressive and eventually fatal hereditary disease that destroys neurons in the areas of the brain involved in
20 emotion, intellect, and movement. The progression of Huntington's disease is characterized by chorea, progressive loss of mental abilities, and the development of personality disorders.

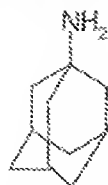
Hyperkinetic movement disorders also include tardive dyskinesia (also known as drug-induced chorea), Tourette's Syndrome, Sydenham's chorea, hemiballism and senile chorea.

25 Tardive dyskinesia is a neurological syndrome caused by the long-term use of neuroleptic drugs. Neuroleptic drugs are generally prescribed for psychiatric disorders such as schizophrenia and bipolar disorder. Tardive dyskinesia is characterized by repetitive, involuntary, purposeless movements. Features of the disorder can include kissing, blowing, lip pursing and tongue protrusion. There are currently no FDA-approved drugs in the United
30 States for the treatment of tardive dyskinesia.

Tourette's Syndrome is an inherited neurological disorder that generally becomes evident in early childhood or adolescence. Tourette's Syndrome is characterized by multiple involuntary motor and vocal muscle contractions, or tics. Existing treatments for Tourette's Syndrome are only moderately efficacious and often have unwanted side effects.

Amantadine is an antiviral agent against prophylactic or symptomatic influenza A in adult. In addition, it also used as an antidyskinetic in the treatment of Parkinson's disease and drug-induced extrapyramidal reactions. It is believed that amantadine blocks dyskinesia in Parkinson's disease by inhibiting the glutamatergic N-methyl-D-aspartate (NMDA)

5 receptors. The structure of 1-aminoadamantane (amantadine — INN) is shown as Formula 1:

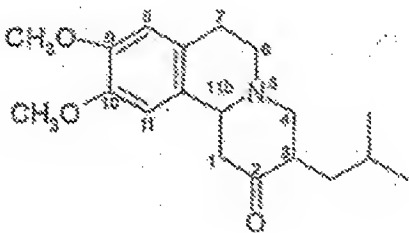


Formula 1

Amantadine has been used for improving choreatic symptoms. The preparation of amantadine and its salts (hydrochloride, phosphate, sulfate, adipate, acetate, succinate, propionate, tartrate, citrate, bicarbonate and lactate salts) is described in GB 1,006,885. The
10 preparation of amantadine, pamoate salt, is described in GB 1,063,366. Amantadine is normally used as hydrochloride.

Amantadine, which blocks the N-methyl-D-aspartate (NMDA) glutamate receptor, was shown to lower chorea scores with oral doses of 400 mg/day (Verhagen Meitman et al. *Neurology*, 59, 694-699 (2002)); or to lower dyskinesia scores with doses of 300 mg/day
15 (Lucetti et al., *Neurology*, 60: 1995-1997 (2003)). However, a complete remission of chorea cannot be achieved with amantadine with the above doses. On the other hand, an increase of amantadine dosage would induce undesired side effects such as psychosis.

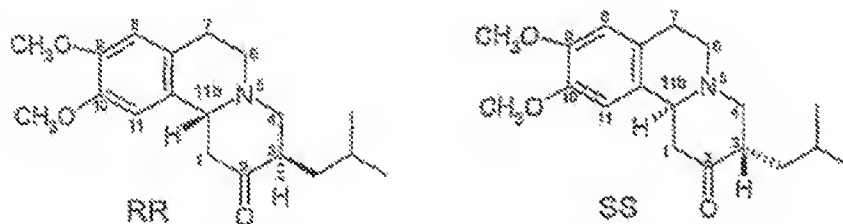
The chemical structure of tetrabenazine, 2-oxo-3-isobutyl-9, 10-dimethoxy-1,2,3,4,6,7-hexahydro-11 β -H-benzo[a]quinolizine (International Non-proprietary Name, INN) is shown as Formula 2 below:



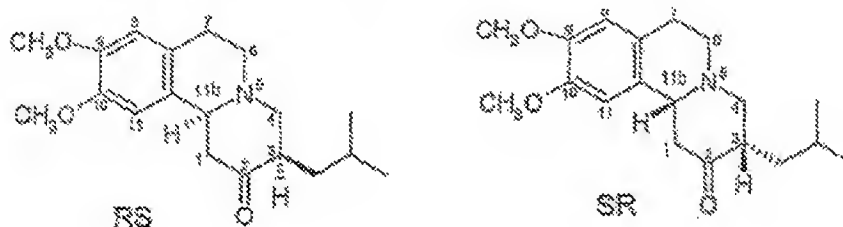
Formula 2

25 Tetrabenazine has chiral centers at the 3 and 11 β carbon atoms and hence can, theoretically, exist in a total of four isomeric forms, as shown in Formula 3 as *RR*, *SS*, *RS* and

SR, wherein RR and SS are trans forms (the hydrogen atoms at the 3-and 11b-positions are in the *trans* relative orientation), and RS and SR are cis forms (the hydrogen atoms at the 3-and 11b-positions are in the *cis* relative orientation):



Cis (the hydrogen atoms at the 3-and 11b-positions are in the *cis* relative orientation):

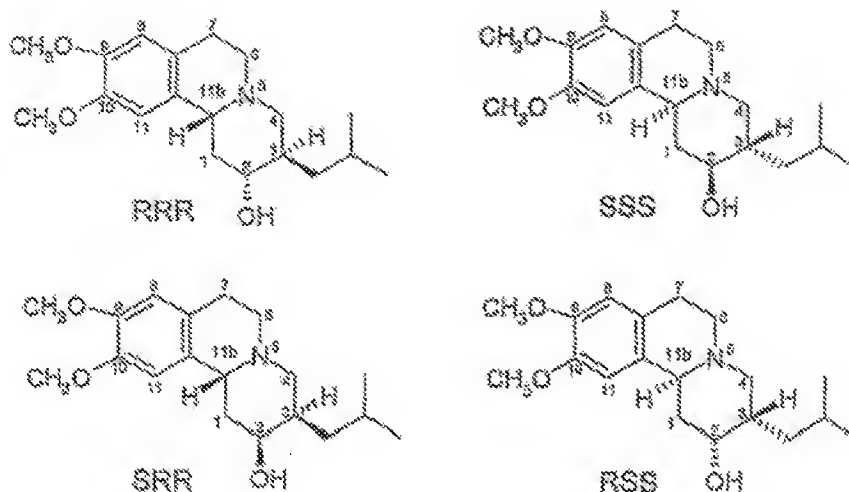


Formula 3

Commercially available tetraabenazine is a racemic mixture of the *RR* and *SS* isomers.

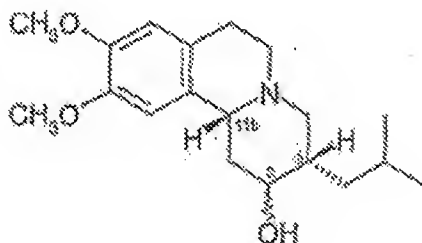
The major metabolite of tetraabenazine is dihydrotetraabenazine (Chemical name: 2-hydroxy-3-(2-methylpropyl)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10- dimethoxy-benzo (a) quinolizina), also known as hydroxytetraabenazine, which is formed by endogenous, stereospecific reduction of the 2-keto group of tetraabenazine.

The structures of the four known dihydrotetraabenazine isomers having a *trans* relative orientation between the hydrogen atoms at the 3 and 11b positions are shown in Formula 4 as RRR, SSS, SRR, and RSS. The 2R, 3R, 11bR (RRR) configuration, also known as (+)- α -dihydrotetraabenazine, is an active metabolite of tetraabenazine. The 2S, 3S, 11bS (SSS) configuration, is also known as (-)- α -dihydrotetraabenazine.



Formula 4

5 The structure of 3, 11b-*cis*- dihydrotetrabenazine is shown below as Formula 5, wherein the hydrogen atoms at the 3-and 11b-positions are in the *cis* relative orientation.



Formula 5

10

There are four isomers of dihydrotetrabenazine having the 3, 11b-*cis* configuration and these are the 2*S*, 3*S*, 11b*R* (SSR) isomer, the 2*R*, 3*R*, 11b*S* (RRS) isomer, the 2*R*, 3*S*, 11b*R* (RSR) isomer and the 2*S*, 3*R*, 11b*S* (SRS) isomer.

The preparation of tetrabenazine and of its salts, in particular the hydrochloride, is described in GB 789,789. The preparation of α -dihydrotetrabenazine and its salts, in particular the hydrochloride, is described in GB 800,969. The preparation of (+)- α -dihydrotetrabenazine is described by Brossi (*Helv. Chim. Acta.*, 41:249-251 (1958)). The preparation of (+)- α -dihydrotetrabenazine is described by Kilbourn (*Eur. J. Pharmacol.*, 278:249-251 (1995)). The preparation of *cis* isomers of dihydrotetrabenazine is described in

20 WO 2005/077946.

Tetrabenazine, a dopamine depletor that works by selectively blocking vesicular monoamine transporter 2 (VMAT2), improves the symptoms associated with a number of hyperkinetic movement disorders. The dose of tetrabenazine in an individual is not fixed and is usually titrated to "best dose", i.e., the dose that gives the best therapeutical effects and the least side effects. Some patients can only tolerate as little as 25 mg per day, whereas other patients can tolerate as high as 150 to 200 mg per day. Tetrabenazine causes a number of dose-related side effects including sedation, depression, parkinsonism, drowsiness, nervousness or anxiety, and insomnia. It is believed that serotonin and nonadrenaline depletion are likely mechanisms of tetrabenazine-induced depression, which has been reported to occur in approximately 15 percent of patients treated with the drug.

There is a need of a new method for treating hyperkinetic movement disorders. It is desirable that the method results in complete remission of hyperkinetic movement disorders. It is also desirable that the method has little or no significant side effects.

SUMMARY OF THE INVENTION

The present invention is directed to a method for treating a hyperkinetic movement disorder in a human patient. The method comprises administering to a patient an effective amount of amantadine, or a salt thereof, and an effective amount of a tetrabenazine compound selected from the group consisting of tetrabenazine, dihydrotetrabenazine, a salt thereof, an isomer thereof, and a combination thereof. The present method is effective in treating chorea, tremor, dystonia, myoclonus, ballismus, tics, Tourette's Syndrome, and hemiballism. The present method is particularly useful in treating chorea associated with Huntington's disease, tardive dyskinesia, and Tourette's syndrome. The present method provides the advantages of achieving significant improvement of a hyperkinetic movement disorder with less side effects.

The present invention further provides a pharmaceutical composition comprising an effective amount of amantadine and an effective amount of a tetrabenazine compound in admixture with a pharmaceutical carrier.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method for treating a hyperkinetic movement disorder in a human patient. The method comprises administering to a patient suffering from a hyperkinetic movement disorder an effective amount of amantadine, or a salt thereof, and an effective amount of a tetrabenazine compound.

Hyperkinetic movement disorders are generally characterized by involuntary, purposeless movements that flow randomly from one body part to another. The present invention is useful in treating hyperkinetic movement disorders including but not limited to chorea, tremor, dystonia, myoclonus, ballismus, tics, Tourette's Syndrome, hemiballism.

5 Chorea includes chorea associated with Huntington's disease, Sydenham's chorea, senile chorea, and chorea induced by metabolic, infectious, inflammatory, vascular, or neurodegenerative disorders, as well as drug-induced chorea (tardive dyskinesia).

The present invention is particularly useful in treating chorea, Tourette's Syndrome, and tardive dyskinesia. The present invention is effective in treating chorea associated with
10 Huntington's disease

The present method administers to a patient a combination of an effective amount of amantadine or its salt, and an effective amount of a tetrabenazine compound.

"A tetrabenazine compound" as used herein, includes tetrabenazine, dihydrotetrabenazine, salts thereof, isomers thereof, and combination thereof. The
15 tetrabenazine isomers suitable for the present method include RR, SS, RS, and SR isomers of Formula 3. The dihydrotetrabenazine isomers suitable for the present method include RRR, SSA, RSS, and SRR isomers of Formula 4, and SSR, RRS, RSR, and SRS isomers of Formula 5. In one embodiment, (+)- α -dihydrotetrabenazine, which is the active metabolite of tetrabenazine, is administered to patients. In general, when (+)- α -dihydrotetrabenazine is
20 administered to patients, it has less dosage variability among different patients compared with tetrabenazine, which is metabolized in the body, thus (+)- α -dihydrotetrabenazine does not need to be titrated in each patient for dosage.

The base compound of amantadine or its pharmaceutically acceptable salts such as hydrochloride, phosphate, sulfate, adipate, acetate, succinate, propionate, tartrate, citrate,
25 bicarbonate, lactate, and pantoate salts; in particular, hydrochloride salt, can be administered to a patient. The base compound of tetrabenazine, dihydrotetrabenazine, or its pharmaceutically acceptable salts such as hydrochloride, phosphate, sulfate, adipate, acetate, succinate, propionate, tartrate, citrate, bicarbonate, lactate, sulphonate, methanesulphonate, ethanesulphonate, benzene sulphonate, toluene sulphonate, camphor sulphonate, and
30 naphthalene sulphonate salts; in particular, hydrochloride salt, can be administered to a patient.

"An effective amount" as used herein, is meant an amount that has a therapeutic effect, which reduces or relieves the symptoms of the hyperkinetic movement disorder being treated. Unless otherwise specified, when an expression like "amantadine or tetrabenazine

compound or a salt thereof" is referred to a dose or a dosage, said dose or dosage refers to the free base. For example, 100 mg of amantadine hydrochloride correspond to 80.58 mg of free base, and 100 mg of tetrabenazine hydrochloride correspond to 89.70 mg of free base.

Applicant has discovered that combined administration of amantadine and
5 tetrabenazine has several advantages that cannot be achieved by the single administration of either amantadine or tetrabenazine. When amantadine and tetrabenazine are administered together to a patient suffering from a hyperkinetic movement disorder, the dosage of each drug can be reduced significantly, thus reducing or eliminating the dose-related side effects such as depression, parkinsonism, drowsiness, nervousness or anxiety, insomnia, and
10 psychosis. Single administration of amantadine or tetrabenazine in general cannot result in complete remission of a hyperkinetic movement disorder, whereas combined administration of amantadine and tetrabenazine often can. In one embodiment of the invention, the combined administration of amantadine and tetrabenazine results in complete remission of chorea, wherein the patient is completely recovered with no residual chorea. In another
15 embodiment of the invention, the combined administration of amantadine and tetrabenazine results in significant improvement of chorea in a patient, which cannot be achieved by a single administration of amantadine or tetrabenazine in the same patient to the same degree.

When amantadine and tetrabenazine are administered together to a patient, each drug cancels out some side effect of the other. For example, amantadine has anti-depressant
20 activity and can counteract the depression side effect of tetrabenazine. Tetrabenazine has anti-psychosis activity and can counteract the psychosis side effect of amantadine.

When amantadine and tetrabenazine are administered together to a patient, the chorea disease progression is decreased.

Amantadine and tetrabenazine can be administered at the same time (concurrently) or
25 at different times (sequentially). When administered concurrently, amantadine and tetrabenazine can be provided in two different compositions, or in a single pharmaceutical composition containing an effective amount of Amantadine and tetrabenazine.

In the present method, the effective amount of amantadine is no greater than 400 mg, preferably no greater than 200 mg, and more preferably, no greater than 150 mg per day. In
30 one embodiment, the effective amount of amantadine is 10-400 mg per day. In another embodiment, the effective amount of amantadine is 50-200 mg per day. In yet another embodiment, the effective amount of amantadine is 75-150 mg per day.

In the present method, the effective amount of a tetrabenazine compound is 10-400 mg per day. In one embodiment, the effective amount of tetrabenazine is 20-200 mg per day.

In another embodiment, the effective amount of tetrabenazine is 30-150 mg per day. In one embodiment, the effective amount of dihydrotetrabenazine is 20-200 mg per day. In another embodiment, the effective amount of dihydrotetrabenazine is 30-150 mg per day. The effective amount of a tetrabenazine compound is preferably no greater than 200mg, and more preferably no greater than 100 mg per day.

The compounds of the present invention can be administered by any of the accepted modes of systemic administration including oral, parenteral, intravenous, intramuscular, and subcutaneous, transdermal, transmucosal, and rectal; with oral administration being preferred.

Any pharmaceutically acceptable mode of administration can be used, including solid, semi-solid, or liquid dosage forms, such as, tablets, suppositories, pills, capsules, powders, granulars, liquids suspensions, injections, or the like, preferably in unit dosage form suitable to single administration of precise dosages, or in sustained or controlled release forms for the prolonged administration of the compound at a predetermined rate. The compositions typically include a conventional pharmaceutical carrier or excipient and the active compound(s) and, in addition, can include other medicinal agents, pharmaceutical agents, carriers, etc. These preparations can be prepared by any conventional methods.

The carriers useful for these preparations include all organic or inorganic carrier materials that are usually used for the pharmaceutical preparations and are inert to the active ingredient. Examples of the carriers suitable for the preparation of tablets capsules, granules and fine granules are diluents such as lactose, starch, sucrose, D-mannitol, calcium sulfate, or microcrystalline cellulose; disintegrators such as sodium carboxymethylcellulose, modified starch, or calcium carboxymethylcellulose; binders such as methylcellulose, gelatin, acacia, ethylcellulose, hydroxypropylcellulose, or polyvinylpyrrolidone; lubricants such as light anhydrous silicic acid, magnesium stearate, talc, or hydrogenated oil; or the like. When formed into tablets, they can be coated in a conventional manner by using the conventional coating agents such as calcium phosphate, carnauba wax, hydroxypropyl methylcellulose, macrogol, hydroxypropyl methylphthalate, cellulose acetate phthalate, titanium dioxide, sorbitan fatty acid ester, or the like.

Examples of carriers suitable for the preparation of syrups are sweetening agents such as sucrose, glucose, fructose, or D-sorbitol; suspending agents such as acacia, tragacanth, sodium carboxymethylcellulose, methylcellulose, sodium alginate, microcrystalline cellulose, or veegum; dispersing agents such as sorbitan fatty acid ester, sodium lauryl sulfate, or polysorbate 80; or the like. When formed into syrups, the conventional flavoring agents,

aromatic substances, preservatives, or the like can optionally be added thereto. The syrups can be in the form of dry syrup that is dissolved or suspended before use.

Examples of carriers used for the preparation of suppositories are cacao butter, glycerin saturated fatty acid ester, glycerogelatin, macrogol, or the like. When formed into
5 suppositories, the conventional surface active agents, preservatives or the like can optionally be admixed.

When formed into injections, the compound is dissolved in a suitable solvent for injection, to which can optionally be added the conventional solubilizers, buffering or pH adjusting agents, isotonic agents, preservatives and other suitable substances. The injections
10 can be in the solid dry preparations, which are dissolved before use.

For solid compositions, conventional non-toxic carriers include, for example mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like can be used. The active compound as defined above can be formulated as suppositories using, for example, polyalkylene glycols such as
15 propylene glycol as a carrier. Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a carrier to form a solution or suspension. If desired, the pharmaceutical composition can also contain minor amounts of non-toxic auxiliary pH buffering agents and the like, for example, sodium acetate, sorbitan
20 monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being
25 treated.

Dosage forms or compositions contain active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier can be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, and can contain 1%-95% active compound(s), preferably
30 5%-50%.

Parenteral administration is generally characterized by injection, whether subcutaneously, intramuscularly, or perineurally. Injectables can be prepared in conventional forms, either as liquid solutions, suspensions, or emulsions. In addition, the pharmaceutical compositions can also contain minor amounts of non-toxic substances such as wetting or

emulsifying agents, auxiliary pH buffering agents and the like, such as, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The percentage of active compound(s) contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound(s) and the needs of the subject.

For delayed release, the compound can be formulated in a pharmaceutical composition, such as in microcapsules formed from biocompatible polymers, nanomilled active compound, or in liposomal carrier systems according to methods known in the art.

For continuous release of active agent, the compound can be covalently conjugated to a water soluble polymer, such as a polylactide or biodegradable hydrogel derived from an amphipathic block copolymer, as described in U.S. Patent No. 5,320,840. Collagen-based matrix implants, such as described in U.S. Patent No. 5,024,841, are also useful for sustained delivery of therapeutics.

The present invention further provides a pharmaceutical composition comprising an effective amount of amantadine and an effective amount of a tetrabenazine compound selected from the group consisting of tetrabenazine, dihydrotetrabenazine, salts thereof, isomers thereof, and combination thereof, in admixture with a pharmaceutical carrier. The effective amount of amantadine in the pharmaceutical composition is 10-400 mg, Preferably 25-200 mg, and more preferably 25-100 mg. The effective amount of a Tetrabenazine compound in the pharmaceutical composition is 10-150 mg, and more preferably 10-75 mg. For example, the pharmaceutical composition comprises 25-200 mg of amantadine and 10-150 mg of tetrabenazine compound. In one embodiment, the pharmaceutical composition is in a oral form and is administered to a patient one, two or three times daily.

The following examples further illustrate the present invention. These examples are intended merely to be illustrative of the present invention and are not to be construed as being limiting.

EXAMPLES

Example 1: Treatment of Huntington's Chorea with amantadine and tetrabenazine

Objectives

- 5 The primary objective of this study is to compare the absolute reduction in chorea in patients treated with amantadine alone, tetrabenazine alone, and amantadine plus tetrabenazine.

Patient population

- At least 10 patients, males and females, ≥ 18 years of age are enrolled in this study. Patients
10 have suffered from Huntington's disease as confirmed by a characteristic movement disorder (chorea), a positive family history, and an expanded cytosine-adenine-guanine (CAG) repeat ($n \geq 37$). Patients have a Total Maximal Chorea Score ≥ 10 from the Unified Huntington's Disease Rating scale (UHDRS, item 12; q12a--12g).

- Patients do not have an unstable or serious medical or psychiatric illness or a total 17-item
15 Hamilton Depression Rating scale (HAM-D) score > 15 . Patients are not concurrently taking dopamine-depleting drugs or dopamine D_2 receptor blockers. Patients do not have untreated depression. Patients are not lacking of caregivers.

Drug Formulation

- 20 Amantadine tablets contain 100 mg of amantadine.
Tetrabenazine tablets contain 12.5 mg of tetrabenazine.

Protocols

1. Baseline Determination
25 Prior to the initiation of treatment, Total Maximal Chorea Score and Clinical Global Impression of each patient are determined.
2. Best Dose Titration
Each patient is first titrated up for "best dose" of tetrabenazine, starting at 12.5 mg per
30 day (one tablet per day). Based on efficacy and depending on tolerability, tetrabenazine is titrated up by 12.5 mg increments (i.e., one tablet) until 75 mg, then up by 25 mg increments until 100 or 200 mg per day. Each patient takes the same dose for 3-7 days (e.g. 5 days), then takes the next higher dose. Dosage is increased over about 7 weeks or until the occurrence of

intolerable side effects. If at any time during the titration phase, intolerance develops in a patient (moderate to severe possibly or probably drug related adverse events), the "best dose" of tetrabenazine of that patient is the patient's previous well-tolerated dose.

3. After the "best dose" of each patient is determined, the patient takes tetrabenazine
5 tablet(s) orally twice a day at the determined "best dose" for at least 5 days. The therapeutic efficacy in each patient is determined at the end of the tetrabenazine treatment.

4. Tetrabenazine is discontinued for one week, such that the effect of tetrabenazine is washed out.

5. Each patient then takes orally one amantadine tablet (100 mg) twice a day for one
10 week. The therapeutic efficacy in each patient is determined at the end of one week.

6. Each patient then takes orally one amantadine tablet (100 mg) and one or more tablets of tetrabenazine at the same time twice a day for a week. The dosage of tetrabenazine in each patient varies, depending on the "best dose" according to the titration. The therapeutic efficacy is determined in each patient at the end of one week.

Therapeutic Efficacy

Therapeutic efficacy is evaluated primarily on the Total Maximal Chorea Score of the UHDRS motor portion (item 12 of the UHDRS; q12a-12g). The secondary efficacy parameters will be the Clinical Global Impression (CGI).

Results

Total Maximal Chorea Scores of each patient (a) before the treatment, (b) after treatment with tetrabenazine alone, (c) after treatment with amantadine alone, and (d) after treatment with the combination of amantadine and tetrabenazine are compared.

Example 2: Treatment of Huntington's Chorea with amantadine and tetrabenazine (Short Protocol)

The objectives, patient population, and drug formulation are the same as those described in Example 1.

Protocols

1. Baseline Determination

Prior to the initiation of treatment, Total Maximal Chorea Score of each patient is determined.

2. Each patient takes tetrabenazine tablet(s) orally at a single dose of 12.5 mg for the first day, 25 mg for the second day, and 50 mg for the third day. Total Maximal Chorea Score of each patient is determined throughout each day (e.g. every two hours).
3. Tetrabenazine is discontinued for one week, such that the effect of tetrabenazine is washed out.
4. Each patient then takes orally one amantadine tablet (100 mg) twice a day for one week. Total Maximal Chorea Score of each patient is determined at the end of each day.
5. Each patient then takes orally one amantadine tablet (100 mg) twice a day and tetrabenazine at a single dose of 12.5 mg for the first day, 25 mg for the second day, and 50 mg for the third day. Total Maximal Chorea Score of each patient is determined throughout each day (e.g. every two hours).

Results

- Total Maximal Chorea Scores of each patient (a) before the treatment, (b) after treatment with tetrabenazine alone, (c) after treatment with amantadine alone, and (d) after treatment with the combination of amantadine and tetrabenazine are compared.

- The invention, and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications can be made therein without departing from the scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude the specification.

WHAT IS CLAIMED IS:

1. A method for treating a hyperkinetic movement disorder in a human patient, which comprises administering to a patient suffering from a hyperkinetic movement disorder an effective amount of amantadine, or a salt thereof, and an effective amount of a tetrabenazine compound selected from the group consisting of tetrabenazine, dihydrotetrabenazine, salts thereof, isomers thereof, and a combination thereof.
2. The method according to Claim 1, wherein said hyperkinetic movement disorder is chorea, tardive dyskinesia, or Tourette's syndrome.
3. The method according to Claim 2, wherein said chorea is chorea associated with Huntington's disease.
4. The method according to Claim 1, wherein said administering is oral administration.
5. The method according to Claim 1, wherein said effective amount of amantadine is no greater than 400 mg per day.
6. The method according to Claim 5, wherein said effective amount of amantadine is no greater than 200 mg per day.
7. The method according to Claim 6, wherein said effective amount of amantadine is no greater than 150 mg per day.
8. The method according to Claim 7, wherein said effective amount of amantadine is no greater than 100 mg per day.
9. The method according to Claim 1, wherein said effective amount of the tetrabenazine compound is no greater than 200 mg per day.
10. The method according to Claim 9, wherein said effective amount of the tetrabenazine compound is no greater than 150 mg per day.
11. The method according to Claim 8, wherein said effective amount of the tetrabenazine compound is no greater than 100 mg per day.

12. The method according to any one of Claims 1-11, wherein said tetrabenazine compound is tetrabenazine, salts thereof, or isomers thereof.
13. The method according to any one of Claims 1-11, wherein said tetrabenazine compound is (+)- α -dihydrotetrabenazine, or salts thereof.
14. The method according to Claims 1-13, wherein said administering is oral administration.
15. A pharmaceutical composition comprising an effective amount of amantadine and an effective amount of a tetrabenazine compound selected from the group consisting of tetrabenazine, dihydrotetrabenazine, salts thereof, isomers thereof, and combination thereof, in admixture with a pharmaceutical carrier.
16. The pharmaceutical composition according to Claim 15, wherein said tetrabenazine compound is tetrabenazine, salts thereof, or isomers thereof.
17. The pharmaceutical composition according to Claim 15, wherein said tetrabenazine compound is (+)- α -dihydrotetrabenazine, or salts thereof.
18. The pharmaceutical composition according to Claim 15, wherein said effective amount of amantadine is 10-400 mg.
19. The pharmaceutical composition according to Claim 18, wherein said effective amount of amantadine is 25-200 mg.
20. The pharmaceutical composition according to Claim 19, wherein said effective amount of amantadine is 25-100 mg.
21. The pharmaceutical composition according to Claim 15, wherein said effective amount of the tetrabenazine compound is 10-200 mg.
22. The pharmaceutical composition according to Claim 21, wherein said effective amount of the tetrabenazine compound is 10-100 mg.
23. The pharmaceutical composition according to Claim 22, wherein said effective amount of the tetrabenazine compound is 10-50 mg.